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CONFORMATIONAL EQUILIBRIA IN BRIDGEHEAD NITROGEN SYSTEMS

T. A. Crabb and R. F. Newton

Department of Chemistry, Portsmouth Polytechnic, Hampshire

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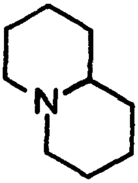
A recent spectroscopic determination[1] of ΔG° values for the *cis* ⇌ *trans*-quinolizidine and *cis* ⇌ *trans*-indolizidine equilibria has brought to light an apparent anomaly. Whereas almost equal values of $\Delta G^{\circ} = -2.6$ kcal/mole and $\Delta G^{\circ} = -2.4$ kcal/mole were found for the quinolizidine (1) and indolizidine (2) equilibria respectively the free energy difference between the carbocyclic analogues *cis*-and *trans*-decalin ($\sim$2.7 kcal/mole favouring the *trans* isomer)[2] and between *cis*-and *trans*-hydrindane[3,4] (0.3 kcal/mole favouring the *trans* isomer) differ by 2.3 kcal/mole. It is the purpose of this communication to provide an explanation for these observations based upon 100 MHz NMR studies on the 8-oxa-1-azabicyclo[4.3.0]nonane system (3)[5].



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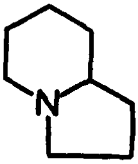

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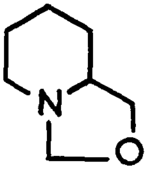

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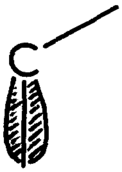
The small enthalpy difference (1.07 ± 0.09 kcal/mole) between *cis*-and *trans*-hydrindane has been interpreted[3,4] in terms of the strain arising from the fusion of the half-chair form of cyclopentane to the cyclohexane ring. A flattening of the six-membered ring in *cis*-hydrindane readily accommodates the 48° torsional angle of the *cis* bonds in the cyclopentane ring but in *trans*-hydrindane considerable strain is involved in accommodating the 72° torsional angle of the corresponding *trans* bonds. Since the ΔG° values quoted above show that indolizidine is appreciably more stable in the *trans* ring fusion than is hydrindane it is reasonable to suppose that the strain present in hydrindane is relieved in <u>trans</u>-indolizidine by a flattening of the readily deformable bridgehead nitrogen atom. A similar deformation was suggested to explain changes in free energies of activation for ring inversion in hexahydropyrimidines[6] and in hexahydro 1,3,5-triazines[7]. Such a flattening of the bridgehead nitrogen atom should be detectable by NMR spectroscopy since the geminal coupling constant (J_{gem}) of the



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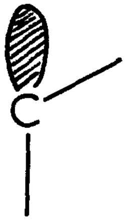

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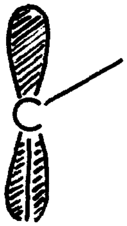

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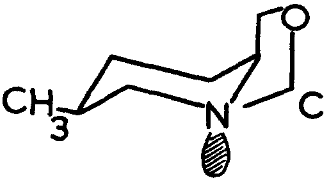
methylene group protons α to a nitrogen atom is sensitive to the relative orientation of the nitrogen lone pair of electrons.[8] It has been shown[9] that when the relative orientation of the methylene group and the lone pair of electrons is as in (4) a more positive value of J_{gem} is observed than when the relative orientation is as in (5).



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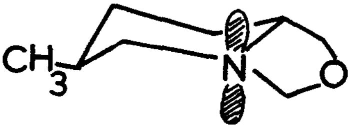

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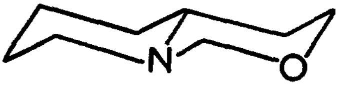

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If in indolizidine flattening about the C-N bonds occurs to minimize the strain then the J_{gem} of the α-methylene protons should be more positive than the "normal" values since increasing the sp^2 hybridization of the nitrogen atom will increase the p character of the lone pair orbital. This will then permit the lone pair to eclipse the axial C-H bond in the six-membered ring (6) and to near eclipse the pseudo-axial C-H in the five-membered ring resulting in a more efficient overlap of the lone pair with the antisymmetric molecular orbital of the methylene group[10] producing a positive change in the value of J_{gem}. The relevant couplings are not available for indolizidine but are readily obtainable for similarly situated protons in *cis* and *trans* fused derivatives of the related 8-oxa-1-azabicyclo[4.3.0]nonane system.

Cis-3,6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane is known to exist predominantly in the *cis*-fused ring conformation[5,11] (7) and J_{gem} for the C2 methylene group is -10.5Hz. *Trans*-3,6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane exists predominantly in the *trans*-fused ring conformation (8) and in this compound the J_{gem} for the C2 methylene group is -6.8Hz. Similar values were found for the analogous protons in the 4-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes. The value of -6.8Hz is the largest J_{gem} ever reported for a methylene group α to a nitrogen atom in a six-membered ring. Normally values of -10 to -12Hz are observed.[9] In addition the J_{gem} of the C9 methylene protons in (8) is extremely large (-0.8Hz), being identical with the value observed for many 1,3-dioxolans[8] in which not only the combined electronegativity of two oxygen atoms is operating but also back donation of electrons from four eclipsing lone pair orbitals. The corresponding J_{gem} in (7) is "normal" (-5Hz). One must therefore postulate an extremely effective overlap between the nitrogen lone pairs and the adjacent antisymmetric methylene molecular orbital in (8) and this can only come about when the lone pair has a high percentage of p character, indicating a flattening of the bridgehead nitrogen atom thereby stabilising the *trans* ring fusion (8).

A similar situation can be envisaged in *trans*-indolizidine although the nitrogen atom in this latter compound may not have the same amount of p character since in (8) the shorter C-O bond length and the presence of oxygen lone pairs in place of C-H bonds may well assist the flattening process.

The values of ΔG° for the *cis* $\rightleftharpoons$ *trans*-quinolizidine equilibria and ΔG° between *cis*-and *trans*-decalin are very similar and this is expected since both systems may exist in strain free conformations. J_{gem} for the C4 methylene group in quinolizidine is -10.8Hz and for the C9 methylene group in *trans*-fused 3-oxa-1-azabicyclo[4.4.0]decane[11] (9); is -10Hz. Both values of J_{gem} are in the "normal" range[9] for methylene protons adjacent to nitrogen in a six-membered ring with the lone pair axial and indicate the absence of appreciable strain in these two bicyclic bridgehead nitrogen compounds.

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